Prenatal Diagnosis of a Fetus With Two Balanced De Novo Chromosome Rearrangements

Philip D. Cotter, Michele Caggana, Judith P. Willner, Arvind Babu, and Robert J. Desnick
Department of Human Genetics, Mount Sinai School of Medicine, New York (P.D.C., M.C., J.P.W., A.B., R.J.D.); and Division of Medical Genetics, Department of Pediatrics, Beth Israel Medical Center, New York (A.B.), New York

Two apparently balanced chromosome rearrangements were identified in a 17-week fetus by analysis of cultured amniocytes. The fetal karyotype was 46,XX,t(2;16) (q33;q24), inv(7)(p15q11.23). Parental karyotypes were normal, indicating a de novo origin of both chromosome rearrangements in the fetus. The risk of phenotypic abnormality from a de novo reciprocal translocation or inversion has been estimated at approximately 7% [Warburton, 1991]. The risk of abnormality in this fetus was estimated to be a minimum of 14%, based on the additive risk of each rearrangement, equivalent to 3.5% per chromosome breakpoint. The pregnancy was terminated because of the risk of abnormality and the detection of intrauterine growth retardation by ultrasound. In the absence of additional experience, the minimum presumed risk of phenotypic abnormality for de novo, multiple or complex chromosome rearrangements identified prenatally may be estimated as the additive risk of the number of chromosome breakpoints involved.

KEY WORDS: prenatal diagnosis, complex chromosome rearrangement, translocation, inversion, amniocentesis, intrauterine growth retardation

INTRODUCTION

The interpretation and counseling of apparently balanced chromosome rearrangements at prenatal diagnosis can be problematic. When the same rearrangement is found in a phenotypically normal parent, the risk of abnormality in the fetus is generally negligible [Gardner and Sutherland, 1989]. However, the interpretation and counseling of de novo, apparently balanced chromosome rearrangements identified by prenatal diagnosis is more difficult, since there is an estimated 7% risk of phenotypic abnormality for a reciprocal translocation or an inversion [Warburton, 1991].

The incidence of de novo chromosome rearrangements identified by amniocentesis was 1/2,000 for reciprocal translocations and 1/10,000 for inversions [Warburton, 1991]. Apparently balanced, de novo rearrangements involving more than two chromosome breaks identified by prenatal diagnosis are rare. Only eight previous cases have been reported (Table I). In this communication, we describe the prenatal diagnosis of two apparently balanced de novo chromosome rearrangements detected in cultured amniocytes.

CLINICAL REPORT

A healthy 30-year-old gravida 1 woman was referred for amniocentesis because of an elevated maternal serum α-fetoprotein level. Fetal growth parameters measured by ultrasound at 17 weeks from the last menstrual period were two weeks behind, suggesting early intrauterine growth retardation. Amniotic fluid α-fetoprotein levels were normal. As shown in Figure 1, cytogenetic analysis of 20 cells from two primary amniotic cell cultures showed a female karyotype in all cells containing a reciprocal translocation between the long arms of chromosomes 2 and 16, and a pericentric inversion of chromosome 7: 46,XX,t(2;16)(q33;q24),inv(7)(p15q11.23). Both rearrangements were apparently balanced. Parental karyotypes from peripheral blood lymphocytes were both normal. Paternity was confirmed using the following VNTR and STS markers: D1S80, D3S1754, D4S1625, D9S58, D13S160, and D14S80 [Genome Data Base, 1995]. Thus, the reciprocal translocation and inversion arose de novo. Neither parent had any known exposure prior to or during the pregnancy.

The couple elected to terminate the pregnancy by dilatation and extraction, preventing further examination for fetal abnormalities. The karyotype was confirmed from fetal kidney obtained at termination.

Received for publication November 24, 1995; revision received February 21, 1996.

Address reprint requests to Dr. R.J. Desnick, Professor and Chairman, Department of Human Genetics, Box 1498, Mount Sinai School of Medicine, New York, NY 10029.

TABLE I. Complex and Multiple De Novo Chromosome Rearrangements Identified by Prenatal Diagnosis*

Reference	Predicted # breaks	Type	Outcome	Phenotype
Bogart et al. [1986]	4	CCR	Liveborn	Normal, but speech delay at 2 ½ yr
Kim et al. [1986]	4	CCR	Termination	Intrauterine growth retardation
Köhler et al. [1986]	3	CCR	Liveborn	Normal at 2 yr
Batista et al. [1993]	9	CCR	Termination	Grossly normal
Sikkema-Raddatz et al. [1995]	7	CCR	Termination	Grossly normal
Sikkema-Raddatz et al. [1996]	5	CCR	Liveborn	Normal at 3 yr
Stoll et al. [1979]	4	MCR	Liveborn	Dysmorphic, developmental delay
Pruggmayer et al. [1990]	4	MCR	Liveborn	Normal at 4 yr
Present case	4	MCR	Termination	Intrauterine growth retardation

*CCR = Complex chromosome rearrangement; MCR = Multiple chromosome rearrangement.

DISCUSSION

Most apparently balanced chromosome rearrangements identified by prenatal diagnosis are familial. If a rearrangement is inherited by the fetus in a balanced way from a normal carrier parent then the risk of a phenotypic abnormality is very low. The identification of de novo, apparently balanced chromosome rearrangements by prenatal diagnosis is more problematic. Warburton [1991] reported an approximately 7% risk of phenotypic abnormality for de novo reciprocal translocations and inversions.

Complex chromosome rearrangements (CCRs) involve two or more chromosomes with three or more chromosome breakpoints [Pai et al., 1980] and include multiple chromosome rearrangements; more than one reciprocal translocation or inversion (MCRs). There have been only eight previous reports of de novo MCRs or CCRs identified at prenatal diagnosis (Table I). Of the five liveborns, three were reported to be normal [Köhler et al., 1986; Pruggmayer et al., 1990; Sikkema-Raddatz et al., 1995]. The case reported by Bogart et al. [1986] appeared normal at 2 ½ years but had speech delay, while the case reported by Stoll et al. [1979] was developmentally delayed and dysmorphic. Two of the fetuses that were terminated were grossly normal [Batista et al., 1993; Sikkema-Raddatz et al., 1995], whereas the case reported here and one previous case [Kim et al., 1986] showed intrauterine growth retardation. In two large surveys, additional cases of de novo MCRs or CCRs at amniocentesis were noted, but no follow-up information was reported [Hook and Cross, 1987; Warburton, 1991].

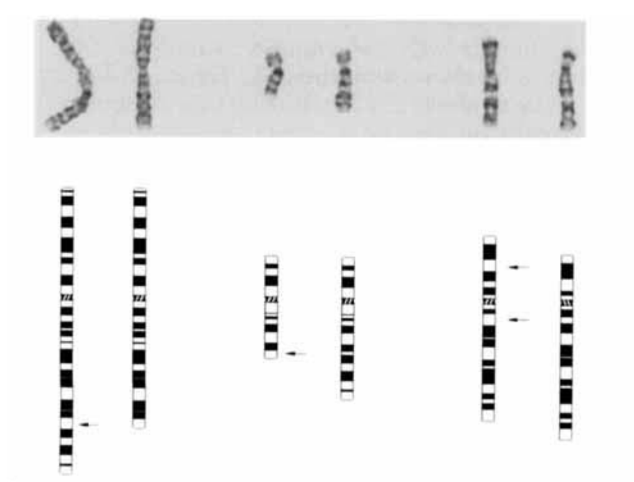

Fig. 1. Partial karyotype (**top**) and ideogram (**bottom**) of the reciprocal translocation [t(2;16)(q33;q24)] and the inversion [inv(7)(p15q11.23)]. Arrows indicate the breakpoints.

Analysis of the previous cases (Table I) would suggest a high risk of abnormality; three of the eight had an abnormality. However, caution should be used in drawing conclusions from such a small sample number with incomplete data. The speech delay in the patient reported by Stoll et al. [1979] may have been unrelated to the chromosome rearrangement. Alternatively, the grossly normal terminations reported by Batista et al. [1993] and Sikkema-Raddatz et al. [1995] may have, had they gone to term, resulted in subtle dysmorphia or developmental delay. Before valid conclusions can be drawn from empirical data, additional cases with follow-up are required. In the absence of such information, it is prudent to estimate the minimum risk of abnormality based on the number of chromosome breaks; the greater the number of breakpoints, the higher the risk of phenotypic abnormality. Such abnormalities are presumed to arise from undetected small deletions, gene disruption, or position effects [Warburton, 1991], all of which would be potentially caused by chromosome breakage and rearrangement.

In cases of MCRs as reported here (an inversion and a reciprocal translocation) or those of Stoll et al. [1979] and Pruggmayer et al. [1990] (two reciprocal translocations) an a priori risk can be estimated from the empirical risks of each event. Thus, for the case reported here, the risk was calculated to be a minimum of 14% based on the combined risk of each rearrangement; a 7% risk each for a de novo reciprocal translocation and an inversion [Warburton, 1991], or 3.5% for each chromosome breakpoint. Similarly, for two reciprocal translocations an a priori risk of approximately 14% would be derived. In these three cases, four chromosome breakpoints were involved.

Gardner and Sutherland [1989] predicted that de novo CCRs would have as high as a 90% risk of phenotypic abnormality. However, one third of reported CCRs are familial [Batista et al., 1993], being inherited from a phenotypically normal balanced CCR carrier. In addi-

tion, normal individuals with balanced CCRs are likely to be under-reported due to ascertainment bias. Thus, the a priori risk for a CCR is likely to be lower than 90%. We suggest that for CCRs resulting from four chromosome breaks (Table I), approximately 14% would seem a reasonable minimum a priori risk estimate (based on the presumed risk for four breakpoint multiple chromosome rearrangements). Case 1 of Sikkema-Raddatz et al. [1995] involved seven chromosome breakpoints and the case reported by Batista et al. [1993] resulted from nine predicted chromosome breaks. These cases would be expected to carry a higher risk of abnormality based on their number of breakpoints; in the range of 25% and 32% for seven and nine breakpoints, respectively. However, the risk figure may be lower if one or more breakpoints occur in a heterochromatic region, as the break is less likely to interrupt a functional sequence. In such cases the possibility of position effects adjacent to the heterochromatic region should also be taken into consideration. Similarly, a lower risk is likely where a breakpoint is located in the short arm of an acrocentric chromosome in CCRs or where a Robertsonian translocation is part of a MCR. Warburton [1991] reported a 3.7% risk of abnormality for de novo Robertsonian translocations. However, to date, there has been no report of a Robertsonian translocation involved in a MCR or CCR.

In the absence of sufficient data from complex or multiple de novo balanced chromosome rearrangements, including long-term follow-up, the risk of phenotypic abnormalities can only be assessed as a function of the number of chromosome breakpoints involved. Thus, when multiple or complex de novo balanced chromosome rearrangements are found, the minimum risk of abnormality may be reasonably estimated from the additive risk of the number of chromosome breakpoints involved.

ACKNOWLEDGMENTS

The authors are grateful to Florina Hristescu and Irina Gershin for expert technical assistance. This work was supported in part by grants from the National Institutes of Health for the Mount Sinai Child Health Research Center (5 P30 HD28822) and for the Mount Sinai General Clinical Research Center (2 M01 RR00071).

REFERENCES

Batista DAS, Tuck-Miller CM, Martinez JE, Kearns WG, Pearson PL, Stetten G (1993): A complex chromosomal rearrangement detected prenatally and studied by fluorescence in situ hybridization. Hum Genet 92:117–121.

Bogart MH, Bradshaw CL, Jones OW, Schanberger JE (1986): Prenatal diagnosis and follow up of a child with a complex chromosome rearrangement. J Med Genet 23:180–183.

Gardner RJM, Sutherland GR (1989): "Chromosome Abnormalities and Genetic Counseling." New York: Oxford University Press,

Genome Data Base GDB™ (1995): "The Human Genome Data Base Project." Baltimore, MD: Johns Hopkins University, World Wide Web <URL:http://gdbwww.gdb.org/gdbdoc/topq.html>.

Hook EB, Cross PK (1987): Rates of mutant and inherited structural cytogenetic abnormalities detected at amniocentesis: Results on about 63,000 fetuses. Ann Hum Genet 51:27–55.

Kim HJ, Perle MA, Bogosian V, Greco A (1986): Prenatal diagnosis of a de novo complex chromosomal rearrangement involving four chromosomes. Prenat Diag 211–216.

Köhler J, Brackertz M, Feige A, Grimm T (1986): Prenatal diagnosis of a complex, balanced rearrangement of chromosomes 7 and 14 in a healthy child with a history of preconceptual X-ray exposure. Prenat Diag 6:389–390.

Pai GS, Thomas GH, Mahoney W, Migeon BR (1980): Complex chromosome rearrangements. Report of a new case and literature review. Clin Genet 18:436–444.

Pruggmayer M, Zoll B, Leipoldt M, Thies U (1990): Prenatal diagnosis and postnatal follow-up of a child with two *de novo* unrelated balanced reciprocal translocations. Prenat Diag 10:337–342.

Sikkema-Raddatz B, Sijmons RH, Tan-Sindhunata MB, Van Der Veen AY, Brunsting R, De Vries B, Beekhuis JR, Bekedam DJ, Van Aken B, De Jong B (1995): Prenatal diagnosis in two cases of *de novo* complex balanced chromosomal rearrangements: Three-year follow-up in one case. Prenat Diag 15:467–73.

Stoll C, Flori E, Macler J, Renaud R (1979): Prenatal diagnosis and postnatal follow-up of an abnormal child with two de novo apparently balanced translocations. Hum Genet 47:221–224.

Warburton D (1991): De novo balanced chromosome rearrangements and extra marker chromosomes identified at prenatal diagnosis: Clinical significance and distribution of breakpoints. Am J Hum Genet 49:995–1013.